compounds in spec

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(FILE 'HOME' ENTERED AT 13:41:40 ON 17 NOV 2004)

FILE 'REGISTRY' ENTERED AT 13:41:54 ON 17 NOV 2004
L1 STRUCTURE UPLOADED
L2 19 S L1
L3 946 S L1 FUL
L4 19 S L3

FILE 'CAPLUS' ENTERED AT 13:43:33 ON 17 NOV 2004
L5 88 S L3

FILE 'REGISTRY' ENTERED AT 13:46:39 ON 17 NOV 2004
L6 STRUCTURE UPLOADED
L7 34 S L6
L8 608 S L6 FUL

FILE 'CAPLUS' ENTERED AT 13:47:02 ON 17 NOV 2004
L9 57 S L8

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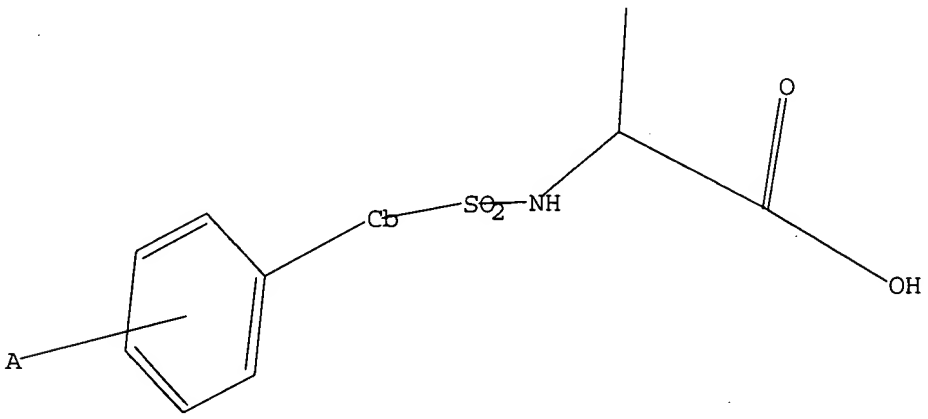
L6 HAS NO ANSWERS
L6 STR




Structure attributes must be viewed using STN Express query preparation.

=> d bib abs 50-57

L9 ANSWER 50 OF 57 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:742171 CAPLUS
DN 129:331047
TI Preparation and use of sulfonylaminocarboxylic acids as medicines
IN Thorwart, Werner; Schwab, Wilfried; Schudok, Manfred; Haase, Burkhard
PA Hoechst Aktiengesellschaft, Germany; Aventis Pharma Deutschland GmbH
SO Eur. Pat. Appl., 48 pp.
CODEN: EPXXDW
DT Patent
LA German
FAN.CNT 1
PATENT NO. KIND DATE APPLICATION NO. DATE

compounds in spec

| | | | | | |
|---|---|---|---|---|---|
| PI | EP 877018 | A1 | 19981111 | EP 1998-108038 | 19980502 |
| | EP 877018 | B1 | 20030502 | | |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| | DE 19719621 | A1 | 19981112 | DE 1997-19719621 | 19970509 |
| | AT 238984 | E | 20030515 | AT 1998-108038 | 19980502 |
| | PT 877018 | T | 20030930 | PT 1998-108038 | 19980502 |
| | ES 2195220 | T3 | 20031201 | ES 1998-108038 | 19980502 |
| | CA 2237099 | AA | 19981109 | CA 1998-2237099 | 19980507 |
| | AU 9864823 | A1 | 19981112 | AU 1998-64823 | 19980508 |
| | AU 732723 | B2 | 20010426 | | |
| | JP 11060551 | A2 | 19990302 | JP 1998-162706 | 19980508 |
| | BR 9801606 | A | 19990518 | BR 1998-1606 | 19980508 |
| | US 6451824 | B1 | 20020917 | US 1998-74693 | 19980508 |
| | RU 2193027 | C2 | 20021120 | RU 1998-108979 | 19980508 |
| | US 2003087945 | A1 | 20030508 | US 2002-170870 | 20020613 |
| PRAI | DE 1997-19719621 | A | 19970509 | | |
| | US 1998-74693 | A3 | 19980508 | | |

OS MARPAT 129:331047

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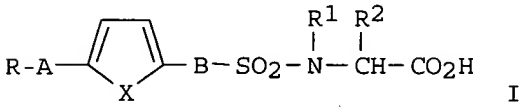

I

AB Title compds. [(I), R = (substituted)phenyl or heteroarom. group; R1 = H, (substituted)alkyl, 2-pyridinyl-methyl; R2 = H, (substituted)alkyl, (un)branched alkenyl, substituted phenyl; R1,R2 together = CO2H-substituted ring; A = bond, O, CY:CY; Y = H, bond; B = (CH2)1-6, O(CH2)1-5, CH:CH, bond; X = CH:CH, O, S], useful as matrix-metalloproteinase inhibitors, were prepared and tested. Thus, DL-homoserine lactone was reacted with PhO-4-C6H4-SO2Cl to give (±)-I [R = Ph; R1 = H; R2 = HOCH2CH2; A = O; B = bond; X = CH:CH(II)] in 73% yield. In in vitro fluorescence extinction tests with stromelysin and neutrophilic collagenase, II had IC50 of 4x10-7 M and 1x10-8M resp.

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 51 OF 57 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:424117 CAPLUS
DN 129:113523
TI Use of matrix metalloproteinase inhibitors for treating neurological disorders and promoting wound healing
IN Bocan, Thomas Michael Andrew; Boxer, Peter Alan; Peterson, Joseph Thomas, Jr.; Schrier, Denis; White, Andrew David
PA Warner-Lambert Co., USA; Bocan, Thomas Michael Andrew; Boxer, Peter Alan; Peterson, Joseph Thomas, Jr.; Schrier, Denis; White, Andrew David
SO PCT Int. Appl., 163 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 9826773 | A1 | 19980625 | WO 1997-US21532 | 19971121 |
| | W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HU, ID, IL, IS, JP, | | | | |

compounds in spec

KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

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|---|---|---|---|---|
| CA 2264692 | AA | 19980625 | CA 1997-2264692 | 19971121 |
| AU 9877353 | A1 | 19980715 | AU 1998-77353 | 19971121 |
| AU 737117 | B2 | 20010809 | | |
| EP 946166 | A1 | 19991006 | EP 1997-949584 | 19971121 |
| EP 946166 | B1 | 20040218 | | |

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

| | | | | |
|---|---|---|---|---|
| BR 9714142 | A | 20000229 | BR 1997-14142 | 19971121 |
| JP 2001507342 | T2 | 20010605 | JP 1998-527715 | 19971121 |
| NZ 334925 | A | 20010629 | NZ 1997-334925 | 19971121 |
| EP 1366765 | A1 | 20031203 | EP 2003-18081 | 19971121 |

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, AL

| | | | | |
|---|---|---|---|---|
| AT 259640 | E | 20040315 | AT 1997-949584 | 19971121 |
| PT 946166 | T | 20040630 | PT 1997-949584 | 19971121 |
| ES 2212142 | T3 | 20040716 | ES 1997-949584 | 19971121 |
| ZA 9711279 | A | 19980623 | ZA 1997-11279 | 19971215 |
| US 6340709 | B1 | 20020122 | US 1999-269123 | 19990319 |
| PRAI US 1996-32753P | P | 19961217 | | |
| EP 1997-949584 | A3 | 19971121 | | |
| WO 1997-US21532 | W | 19971121 | | |

OS MARPAT 129:113523

AB Matrix metalloproteinase inhibitors 4-RC6H4SO2NHCHR1COR2 [R = (un)substituted Ph; R1 = alkyl, phenylalkyl, phenyl; R2 = OH, alkoxy, NHOH] and 4-RC6H4C(:NR3)CR4R5CR6R7COR8 [R3 = (un)substituted OH, NH2; R4-R7 = H, F, (un)substituted alkyl; R8 = OH, SH] are useful for preventing and treating neurol. disorders, especially Alzheimer's, huntington's, and Parkinson's diease and amyotropic lateral sclerosis, and in promoting wound healing. IC50 for matrix metalloproteinase inhibition are reported for a number of compds. Formulations containing (R)-4-(4-NCC6H4)C6H4SO2NHCH(CO2H)CH2Ph, (S)-4-(4-H2NC6H4)C6H4SO2NHCH(CO2H)CH2C6H4OEt-3, and 4-(4-BrC6H4)C6H4SO2NHCH(CO2H)CHMe2 are reported.

RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 52 OF 57 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:402296 CAPLUS
DN 129:76499
TI Method for treating and preventing heart failure and ventricular dilation
IN Peterson, Joseph T., Jr.
PA Warner-Lambert Co., USA
SO PCT Int. Appl., 178 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 9825597 | A2 | 19980618 | WO 1997-US21934 | 19971202 |
| WO 9825597 | A3 | 20001012 | | |

W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR,

compounds in spec

| | | | | | |
|---|---|---|---|---|---|
| | GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| | CA 2263886 | AA | 19980618 | CA 1997-2263886 | 19971202 |
| | AU 9855906 | A1 | 19980703 | AU 1998-55906 | 19971202 |
| | AU 741768 | B2 | 20011206 | | |
| | BR 9714385 | A | 20000516 | BR 1997-14385 | 19971202 |
| | EP 1028716 | A1 | 20000823 | EP 1997-952246 | 19971202 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| | NZ 334897 | A | 20010223 | NZ 1997-334897 | 19971202 |
| | JP 2001526631 | T2 | 20011218 | JP 1998-526758 | 19971202 |
| | ZA 9711004 | A | 19981005 | ZA 1997-11004 | 19971208 |
| | US 5948780 | A | 19990907 | US 1997-987167 | 19971208 |
| | NO 9902769 | A | 19990809 | NO 1999-2769 | 19990608 |
| | KR 2000057444 | A | 20000915 | KR 1999-705070 | 19990608 |
| PRAI | US 1996-32631P | P | 19961209 | | |
| | WO 1997-US21934 | W | 19971202 | | |

OS MARPAT 129:76499

AB Matrix metalloproteinase inhibitors are useful for preventing and treating heart failure, and ventricular dilation in mammals. Thus, 2-(4'-bromobiphenyl-4-sulfonylamino)-3-methylbutyric acid was effective in protecting pigs in the pacing-induced heart failure model.

L9 ANSWER 53 OF 57 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:352635 CAPLUS
DN 129:32284
TI Biphenysulfonamide matrix metalloproteinase inhibitors
IN O'Brien, Patrick Michael; Sliskovic, Drago Robert
PA Warner-Lambert Co., USA
SO U.S., 8 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | US 5756545 | A | 19980526 | US 1997-844598 | 19970421 |
| PRAI | US 1997-844598 | | 19970421 | | |

OS MARPAT 129:32284
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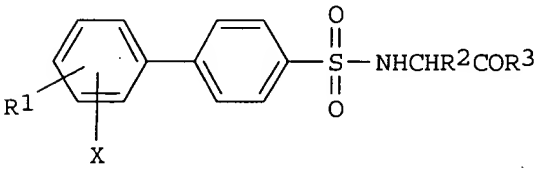


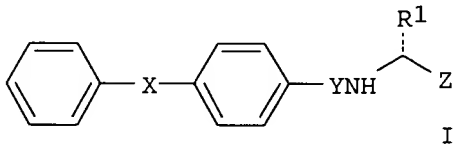

I

AB Compds. I (X = H, halo; R1 = alkyl, halo, nitro, amino, cyano, alkoxy, and alkoxycarbonyl; R2 = alkyl and substituted alkyl; and R3 = OH or NHOH) are useful for inhibiting matrix metalloproteinase enzymes in animals, and as such, prevent and treat diseases resulting from the breakdown of connective tissues. Sulfonation of 4-bromobiphenyl with chlorosulfonic acid, chlorination with POCl3, esterification with L-valine tert-Bu ester, and hydrolysis with trifluoroacetic acid gave (S)-2-(4'-Bromobiphenyl-4-sulfonylamino)-3-methylbutyric acid with 96% yield and m.p.

compounds in spec

192-193°.
RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 54 OF 57 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:66723 CAPLUS
DN 128:188290
TI Highly Selective and Orally Active Inhibitors of Type IV Collagenase (MMP-9 and MMP-2): N-Sulfonylamino Acid Derivatives
AU Tamura, Yoshinori; Watanabe, Fumihiko; Nakatani, Takuji; Yasui, Ken; Fuji, Masahiro; Komurasaki, Tadafumi; Tsuzuki, Hiroshige; Maekawa, Ryuji; Yoshioka, Takayuki; Kawada, Kenji; Sugita, Kenji; Ohtani, Mitsuaki
CS Shionogi Research Laboratories, Shionogi Co. Ltd., Osaka, 553, Japan
SO Journal of Medicinal Chemistry (1998), 41(4), 640-649
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
GI

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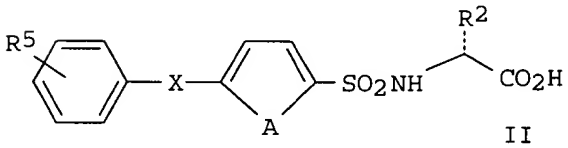


II

AB Various N-sulfonylamino acid derivs., e.g. I (R1 = PhCH2, X = bond, Y = SO2, CO, Z = CONHOH, CO2H; R1 = indol-3-ylmethyl, X = bond, Y = SO2, Z = CONHOH, CO2H; R1 = Me2CH, X = O, Y = SO2, Z = CONHOH, CO2H) and II (R2 = indol-3-ylmethyl, R5 = H, OMe-4, OMe-3, A = CH:CH, X = bond; R2 = indol-3-ylmethyl, R5 = Me-4, A = S, X = bond; R2 = CHMe2, R5 = OMe-4, SMe-4, A = CH:CH, X = bond; R2 = CHMe2, R5 = OMe-4, A = S, X = bond; R2 = indol-3-ylmethyl, R5 = H, Me-4, CO2H-4, A = CH:CH, X = C.tplbond.C; R2 = indol-3-ylmethyl, R5 = NO2-2, NO2-4, Me-4, A = S, X = C.tplbond.C; R2 = CHMe2, R5 = Me-4, A = CH:CH, S, X = C.tplbond.C; R2 = CH2Ph, R5 = OMe-4, A = CH:CH, S, X = C.tplbond.C), were synthesized and evaluated for their in vitro and in vivo activities to inhibit type IV collagenase (MMP-9 and MMP-2). When the amino acid residue and the sulfonamide moiety were modified, their inhibitory activities were greatly affected by the structure of the sulfonamide moiety. A series of aryl sulfonamide derivs. containing biaryl, tetrazole, amide, and triple bond were found to be potent and highly selective inhibitors of MMP-9 and MMP-2. In addition, these compds. were orally active in animal models of tumor growth and metastasis. These results revealed the potential of the N-sulfonylamino acid derivs. as a new type of candidate drug for the treatment of cancer.
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 55 OF 57 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:776147 CAPLUS
DN 128:48054

compounds in spec

TI Biphenylsulfonamide matrix metalloproteinase inhibitors
IN O'Brien, Patrick Michael; Sliskovic, Drago Robert
PA Warner-Lambert Company, USA
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 9744315 | A1 | 19971127 | WO 1997-US6801 | 19970424 |
| | W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GH, HU, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| | CA 2253342 | AA | 19971127 | CA 1997-2253342 | 19970424 |
| | AU 9726803 | A1 | 19971209 | AU 1997-26803 | 19970424 |
| | AU 713286 | B2 | 19991125 | | |
| | EP 901466 | A1 | 19990317 | EP 1997-918788 | 19970424 |
| | EP 901466 | B1 | 20011031 | | |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI | | | | |
| | CN 1219166 | A | 19990609 | CN 1997-194719 | 19970424 |
| | CN 1077885 | B | 20020116 | | |
| | BR 9710841 | A | 19990817 | BR 1997-10841 | 19970424 |
| | NZ 332711 | A | 20000623 | NZ 1997-332711 | 19970424 |
| | JP 2000511175 | T2 | 20000829 | JP 1997-542377 | 19970424 |
| | AT 207891 | E | 20011115 | AT 1997-918788 | 19970424 |
| | ES 2167733 | T3 | 20020516 | ES 1997-918788 | 19970424 |
| | SK 282863 | B6 | 20021203 | SK 1998-1577 | 19970424 |
| | EE 3965 | B1 | 20030217 | EE 1998-397 | 19970424 |
| | PL 186416 | B1 | 20040130 | PL 1997-329929 | 19970424 |
| | CZ 294063 | B6 | 20040915 | CZ 1998-3668 | 19970424 |
| | ZA 9704223 | A | 19971210 | ZA 1997-4223 | 19970515 |
| | BG 63940 | B1 | 20030731 | BG 1998-102918 | 19981112 |
| | NO 9805326 | A | 19990114 | NO 1998-5326 | 19981116 |
| | KR 2000011095 | A | 20000225 | KR 1998-709253 | 19981116 |
| | HK 1019585 | A1 | 20020531 | HK 1999-104791 | 19991027 |
| PRAI | US 1996-17460P | P | 19960517 | | |
| | WO 1997-US6801 | W | 19970424 | | |

OS MARPAT 128:48054
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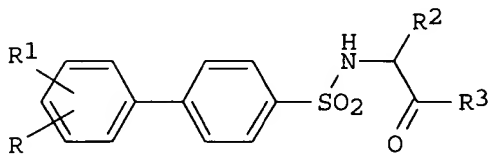


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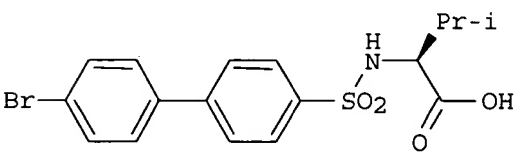


II

compounds in spec

AB Title compds. I [R = H, halo; R1 = alkyl, halo, NO2, amino, aminoalkyl, cyano, alkoxy, alkoxycarbonyl, etc.; R2 = H, (un)substituted alkyl; and R3 = OH, alkoxy, or NHOH], are useful for inhibiting matrix metalloproteinase enzymes in animals, and as such, prevent and treat diseases resulting from the breakdown of connective tissues. For instance, 4-BrC6H4Ph underwent 4'-sulfonation (79%), conversion of the resultant sulfonic acid to the sulfonyl chloride (69%), sulfonamidation with H-Val-OtBu.HCl (60%), and deprotection of the ester (96%), to give title compound II. In an in vitro test for inhibition of the hydrolysis of thiopeptolide by collagenase or gelatinase B, II gave IC50 values of 3.24 and 8.34 μM, resp.

L9 ANSWER 56 OF 57 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:513624 CAPLUS
DN 127:162119
TI Preparation of N-sulfonylamino acid derivatives as metalloproteinase inhibitors
IN Watanabe, Fumihiko; Tsuzuki, Hiroshige; Ohtani, Mitsuaki
PA Shionogi and Co., Ltd., Japan
SO PCT Int. Appl., 128 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 9727174 | A1 | 19970731 | WO 1997-JP126 | 19970122 |
| | W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| | CA 2242416 | AA | 19970731 | CA 1997-2242416 | 19970122 |
| | AU 9713195 | A1 | 19970820 | AU 1997-13195 | 19970122 |
| | AU 715764 | B2 | 20000210 | | |
| | CN 1214041 | A | 19990414 | CN 1997-193226 | 19970122 |
| | BR 9707010 | A | 19990720 | BR 1997-7010 | 19970122 |
| | EP 950656 | A1 | 19991020 | EP 1997-900747 | 19970122 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| | NZ 325939 | A | 20000623 | NZ 1997-325939 | 19970122 |
| | JP 2001316254 | A2 | 20011113 | JP 2001-69135 | 19970122 |
| | SK 282995 | B6 | 20030109 | SK 1998-984 | 19970122 |
| | RU 2198656 | C2 | 20030220 | RU 1998-115659 | 19970122 |
| | TW 575547 | B | 20040211 | TW 1997-86100862 | 19970127 |
| | NO 9803376 | A | 19980914 | NO 1998-3376 | 19980722 |
| | US 6150394 | A | 20001121 | US 1998-120378 | 19980722 |
| | US 6207698 | B1 | 20010327 | US 1998-120197 | 19980722 |
| | US 6235768 | B1 | 20010522 | US 1999-307818 | 19990510 |
| | AU 738793 | B2 | 20010927 | AU 2000-30222 | 20000501 |
| | US 6441021 | B1 | 20020827 | US 2000-710904 | 20001114 |
| | US 2003139379 | A1 | 20030724 | US 2002-188115 | 20020703 |
| | US 2003225043 | A1 | 20031204 | US 2002-290245 | 20021108 |
| PRAI | JP 1996-30082 | A | 19960123 | | |
| | JP 1996-213555 | A | 19960813 | | |
| | JP 1997-526728 | A3 | 19970122 | | |
| | WO 1997-JP126 | W | 19970122 | | |
| | US 1998-120197 | A3 | 19980722 | | |

compounds in spec

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| | US 1998-120383 | A1 | 19980722 |
| | US 2000-710094 | B3 | 20001113 |

OS MARPAT 127:162119

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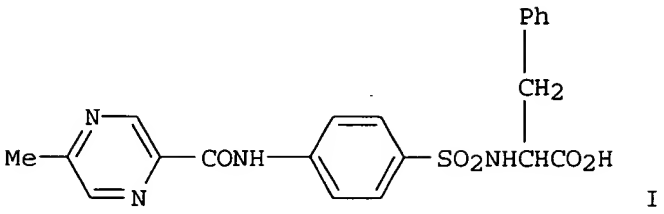


I

AB The title compds. R5R4R3SO2NR2CHR1COY [R1 = (un)substituted alkyl, aryl, aralkyl, heteroaryl, etc.; R2 = H, (un)substituted alkyl, etc.; R3 = single bond, (un)substituted arylene, etc.; R4 = single bond, CH:CH, C.tplbond.C, CO, CONH, N:N, NHCONH, NHCO, O, S, SO2NH, etc.; R5 = (un)substituted alkyl, cycloalkyl, etc.; Y = NHOH, OH; a proviso is given] are prepared The title compound (R)-I in vitro showed IC50 of 3.95 μM against MMP-9 (gelatinase B).

L9 ANSWER 57 OF 57 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1997:69816 CAPLUS

DN 126:89360

TI Preparation of [(isoxazolinylalkanoyl)amino]alkanoates and analogs as integrin antagonists

IN Voss, Matthew Ernst; Jadhav, Prabhakar Kondaji; Smallheer, Joanne Marie; Batt, Douglas Guy; Pitts, William John; Wityak, John

PA Du Pont Merck Pharmaceutical Company, USA

SO PCT Int. Appl., 331 pp.
CODEN: PIXXD2

DT Patent

LA English

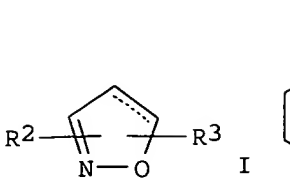
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 9637492 | A1 | 19961128 | WO 1996-US7646 | 19960524 |
| | W: AM, AT, AU, AZ, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, HU, JP, KG, KR, KZ, LT, LU, LV, MD, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, UA, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| | US 5710159 | A | 19980120 | US 1996-647132 | 19960509 |
| | CA 2221980 | AA | 19961128 | CA 1996-2221980 | 19960524 |
| | AU 9658762 | A1 | 19961211 | AU 1996-58762 | 19960524 |
| | ZA 9604195 | A | 19971124 | ZA 1996-4195 | 19960524 |
| | EP 828737 | A1 | 19980318 | EP 1996-920476 | 19960524 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| | JP 11506436 | T2 | 19990608 | JP 1996-535899 | 19960524 |
| PRAI | US 1995-450646 | A | 19950525 | | |
| | US 1995-455768 | A | 19950531 | | |
| | US 1996-647132 | A | 19960509 | | |
| | WO 1996-US7646 | W | 19960524 | | |

OS MARPAT 126:89360

GI

compounds in spec

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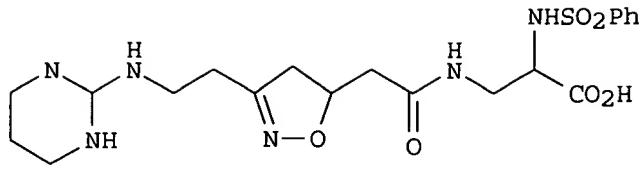



II

AB Title compds. [(addnl.-substituted) I; R2 = Z2Z1R1; R1 = N-containing heterocyclyl; R3 = Z3ZR; R = CO2H, alkoxycarbonyl, SO3H, CONHNHSO2CF3, etc.; Z = bond (un)substituted alkylene; Z1 = bond, (O- or N-interrupted)alkylene, CO, alkanoyl(alkyl), NHCO, etc.; Z2 = bond, alkylene, phenylene, etc.; Z3 = (alkylene)carbonylimino(alkyl), etc.; dashed line = optional bond] were prepared as integrin antagonists (no data). Thus, R4(CH2)3CH:NOH (R4 = phthalimido)(preparation given) was chlorinated and the product cyclocondensed with CH2:CHCH2CO2CMe3 to give, after deprotection, tert-Bu 3-(3-aminopropyl)-2-isoxazoline-5-acetate. The latter was N-alkylated with 2-methylthio-3,4,5,6-tetrahydropyrimidine hydroiodide to give, after saponification, amidation by H2NCH2CH(NHSO2Ph)CO2Me, and saponification, title compound II.

=>

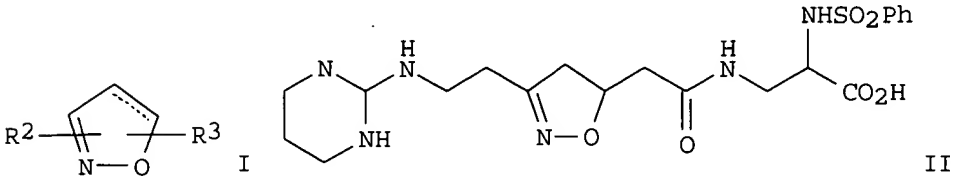
compounds in spec

=> d bib abs hitstr 57

L9 ANSWER 57 OF 57 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:69816 CAPLUS
DN 126:89360
TI Preparation of [(isoxazolinylalkanoyl)amino]alkanoates and analogs as integrin antagonists
IN Voss, Matthew Ernst; Jadhav, Prabhakar Kondaji; Smallheer, Joanne Marie; Batt, Douglas Guy; Pitts, William John; Wityak, John
PA Du Pont Merck Pharmaceutical Company, USA
SO PCT Int. Appl., 331 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 9637492 | A1 | 19961128 | WO 1996-US7646 | 19960524 |
| | W: AM, AT, AU, AZ, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, HU, JP, KG, KR, KZ, LT, LU, LV, MD, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, UA, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| | US 5710159 | A | 19980120 | US 1996-647132 | 19960509 |
| | CA 2221980 | AA | 19961128 | CA 1996-2221980 | 19960524 |
| | AU 9658762 | A1 | 19961211 | AU 1996-58762 | 19960524 |
| | ZA 9604195 | A | 19971124 | ZA 1996-4195 | 19960524 |
| | EP 828737 | A1 | 19980318 | EP 1996-920476 | 19960524 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| | JP 11506436 | T2 | 19990608 | JP 1996-535899 | 19960524 |
| PRAI | US 1995-450646 | A | 19950525 | | |
| | US 1995-455768 | A | 19950531 | | |
| | US 1996-647132 | A | 19960509 | | |
| | WO 1996-US7646 | W | 19960524 | | |

OS MARPAT 126:89360
GI




AB Title compds. [(addnl.-substituted) I; R2 = Z2Z1R1; R1 = N-containing heterocyclyl; R3 = Z3ZR; R = CO2H, alkoxycarbonyl, SO3H, CONHNHSO2CF3, etc.; Z = bond (un)substituted alkylene; Z1 = bond, (O- or N-interrupted)alkylene, CO, alkanoyl(alkyl), NHCO, etc.; Z2 = bond, alkylene, phenylene, etc.; Z3 = (alkylene)carbonylimino(alkyl), etc.; dashed line = optional bond] were prepared as integrin antagonists (no data). Thus, R4(CH2)3CH:NOH (R4 = phthalimido)(preparation given) was chlorinated and the product cyclocondensed with CH2:CHCH2CO2CMe3 to give, after deprotection, tert-Bu 3-(3-aminopropyl)-2-isoxazoline-5-acetate. The latter was N-alkylated with 2-methylthio-3,4,5,6-tetrahydropyrimidine hydroiodide to give, after saponification, amidation by H2NCH2CH(NHSO2Ph)CO2Me,

compounds in spec

and saponification, title compound II.

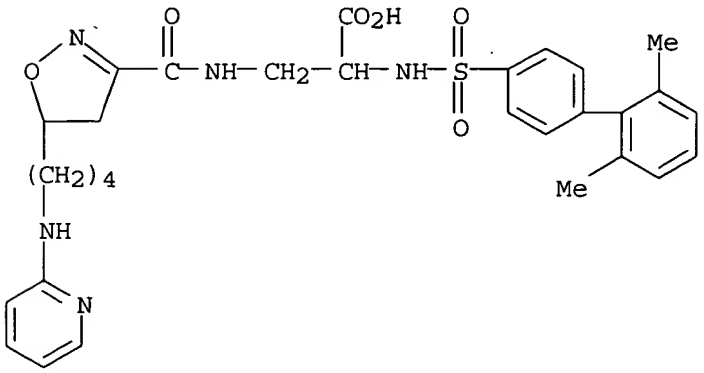
IT **185560-79-6P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of [(isoxazolinylalkanoyl)amino]alkanoates and analogs as integrin antagonists)

RN 185560-79-6 CAPLUS

CN Alanine, 3-[[[4,5-dihydro-5-[4-(2-pyridinylamino)butyl]-3-isoxazolyl]carbonyl]amino]-N-[(2',6'-dimethyl[1,1'-biphenyl]-4-yl)sulfonyl]- (9CI) (CA INDEX NAME)



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L4           19 S L3

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L12          15 S L10 FUL

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L10             STR
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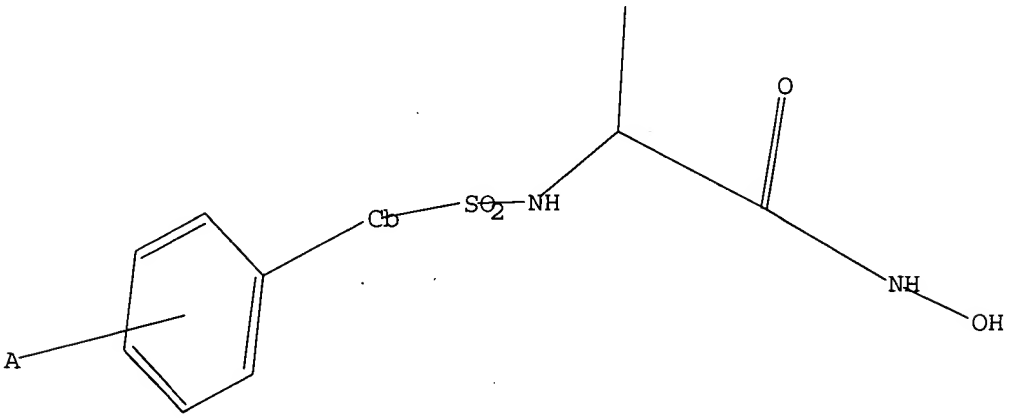


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Structure attributes must be viewed using STN Express query preparation.


=> d bib abs hitstr 1-6

L13  ANSWER 1 OF 6  CAPLUS  COPYRIGHT 2004 ACS on STN
AN   2003:734673  CAPLUS
DN   139:240320
TI   Method for characterizing metabolites using hydrogen/deuterium exchange
IN   Lam, Wing Wah; Ramanathan, Ragulan
PA   Warner-Lambert Company LLC, USA
SO   Eur. Pat. Appl., 42 pp.
```

CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

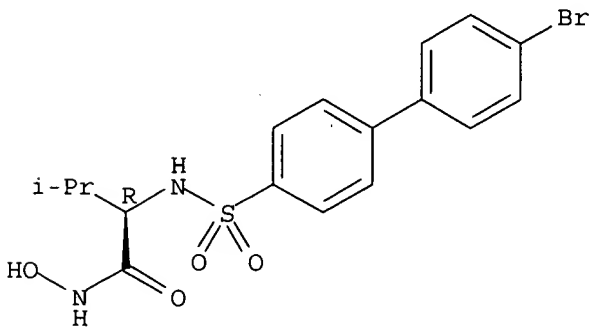
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI EP 1345028 | A1 | 20030917 | EP 2003-4825 | 20030305 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| WO 2003076930 | A1 | 20030918 | WO 2003-IB883 | 20030303 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2003175979 | A1 | 20030918 | US 2003-387613 | 20030313 |
| JP 2004028993 | A2 | 20040129 | JP 2003-68691 | 20030313 |
| PRAI US 2002-364373P | P | 20020314 | | |

AB A system and method for performing hydrogen/deuterium (H/D) exchange in an electrospray ionization (ESI) source is described. The system includes a liquid chromatograph-mass spectrometer (LC-MS), which is equipped with an ESI source that provides for introduction of a sheath liquid The resulting system employs deuterated solvent, such as deuterium oxide, as the sheath liquid, which allows H/D exchange expts. to be performed online. This directly provides information for determining the number and position of exchangeable hydrogens, aiding in the elucidation of the structures of drug metabolites. To demonstrate the usefulness of the invention, the hydrogen/deuterium exchange in the metabolites of PD 0200126 was examined

IT **261625-46-1**, PD 0200126
RL: ANT (Analyte); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)
(method for characterizing drug metabolites using hydrogen/deuterium exchange and liquid chromatograph-mass spectrometer with electrospray ionization source and deuterated sheath liquid applied to metabolism of PD 0200126)

RN 261625-46-1 CAPLUS
CN Butanamide, 2-[[(4'-bromo[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3-methyl-, (2R)- (9CI) (CA INDEX NAME)

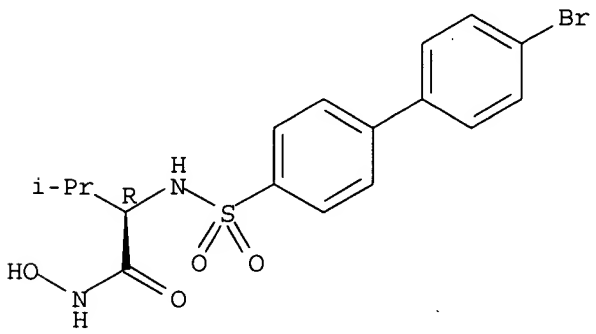
Absolute stereochemistry.




RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:249562 CAPLUS
DN 137:210343
TI In electrospray ionization source hydrogen/deuterium exchange LC-MS and LC-MS/MS for characterization of metabolites
AU Lam, Wing; Ramanathan, Ragu
CS Department of Pharmacokinetics, Dynamics, and Metabolism, Pfizer Global Research and Development, Ann Arbor, MI, USA
SO Journal of the American Society for Mass Spectrometry (2002), 13(4), 345-353
CODEN: JAMSEF; ISSN: 1044-0305
PB Elsevier Science Inc.
DT Journal
LA English
AB A new method is described for performing hydrogen/deuterium (H/D) exchange in an electrospray ionization (ESI) source. The use of liquid chromatog. (LC)-mass spectrometer equipped with an ESI source and deuterium oxide (D2O) as the sheath liquid allows H/D exchange expts. to be performed online. This directly provides information for determining the number and position of exchangeable hydrogens, aiding in the elucidation of the structures of drug metabolites. To demonstrate the utility of this method, LC-mass spectrometry (MS) and LC-MS/MS expts. were performed using either H2O or D2O as sheath liquid on a matrix metalloprotease (MMP) inhibitor (PD 0200126) and its metabolites. Examination of the mass shift of the deuterated mol. from that of the protonated mol. allowed the number of exchangeable protons to be determined Interpretation of the product-ion-spectra helped to determine the location of the exchanged protons and assisted in the assignment of the site(s) of modification for each metabolite.
IT **261625-46-1**, PD 0200126
RL: ANT (Analyte); PKT (Pharmacokinetics); ANST (Analytical study); BIOL (Biological study)
(in electrospray ionization source hydrogen/deuterium exchange LC-MS and LC-MS/MS for characterization of metabolites)
RN 261625-46-1 CAPLUS
CN Butanamide, 2-[[(4'-bromo[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.




RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:611767 CAPLUS
DN 135:180946
TI Preparation of sulfonylamino acid derivatives and sulfonylamino hydroxamic acid derivatives as inhibitors of matrix metalloproteinases
IN Kukkola, Paivi Jaana; Robinson, Leslie Anne; Nakajima, Motowo; Sakaki,

Junichi
PA Novartis A.-G., Switz.
SO U.S., 38 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI US 6277987 | B1 | 20010821 | US 1999-243854 | 19990203 |
| PRAI US 1998-135514P | P | 19980204 | | |

OS MARPAT 135:180946
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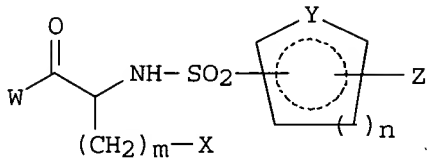


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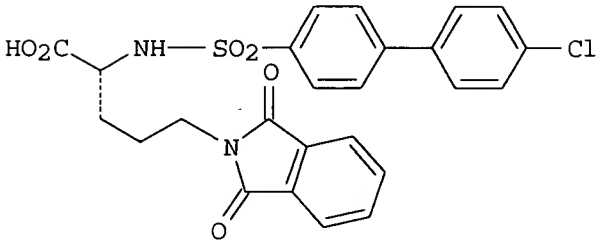



II

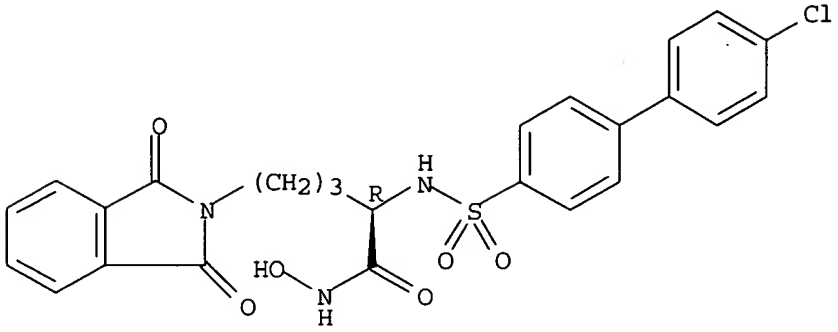
AB Title compds. I [W = OH, NHOH; X = heterocycle with N such that X is attached to (CH2)m group by a ring N, CONR2R3, NR1COR2, NR1SO2R2, NR1CONR2R3, NR1CO2R4, heteroarylthio, alkylthio, arylalkylthio, heteroarylalkylthio, heterocycloalkylalkylthio, heterocycloalkylthio, arylthio; Y = C, N, O, S provided when Y = C, n = 2; Z = alkyl, aryl, alkoxy, aryloxy, aralkoxyaryl, aralkoxyheteroaryl, heteroaryl, heterocycloalkyl, heteroaryloxy, CONR2N3, NR1COR2, NR1CONR2R3, OCONR2R3, NR1CO2R4, SO2R2; R1 = H, alkyl, heterocycloalkylalkyl, aralkyl, heteroarylalkyl; R2, R3 = R1, aryl, heteroaryl; R2R3 = 5- to 7-membered ring which may optionally contain O, N and S; R4 = alkyl, heterocycloalkylalkyl, aralkyl, aryl, heteroaryl; m = 1-6; n = 1, 2] were prepared For example, the synthesis of sulfonylamino acid II involved the following steps: coupling of (R)-BocNHCH(CH2CH2CH2I)CO2CMe3 (prepared in four steps from D-glutamic acid) with phthalimide, removal of the Boc group, coupling with 4'-chlorobiphenyl-4-sulfonyl chloride, and finally, removal of the tert-Bu ester. II inhibited stromelysin and collagenase-3 with IC50 = 130 and 4 nM, resp.

IT **240135-19-7P 240135-35-7P 240135-36-8P**
**240135-47-1P 240135-50-6P 240135-51-7P**
**240135-55-1P 240135-58-4P 240135-62-0P**
**355021-36-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of sulfonylamino acids and sulfonylamino hydroxamic acids as inhibitors of matrix metalloproteinases)

RN 240135-19-7 CAPLUS
CN 2H-Isoindole-2-pentanamide, α-[[(4'-chloro[1,1'-biphenyl]-4-

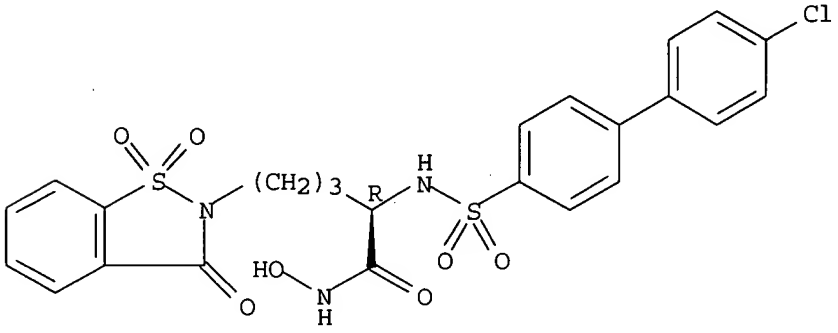
yl)sulfonyl]amino]-1,3-dihydro-N-hydroxy-1,3-dioxo-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



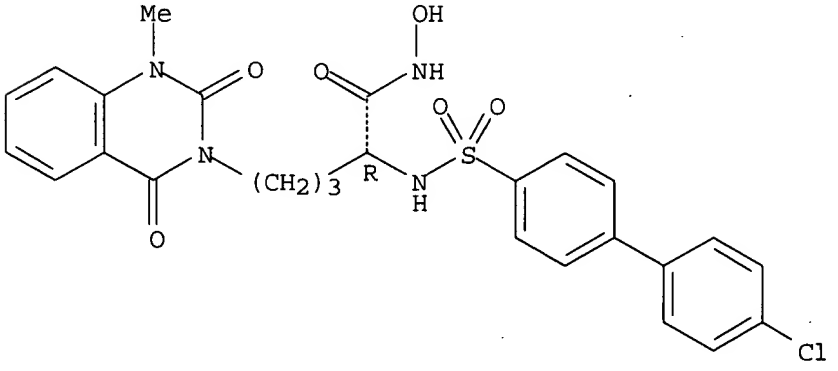
RN 240135-35-7 CAPLUS
CN 1,2-Benzisothiazole-2(3H)-pentanamide, α-[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3-oxo-, 1,1-dioxide, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 240135-36-8 CAPLUS
CN 3(2H)-Quinazolinepentanamide, α-[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-1,4-dihydro-N-hydroxy-1-methyl-2,4-dioxo-, (αR)- (9CI) (CA INDEX NAME)

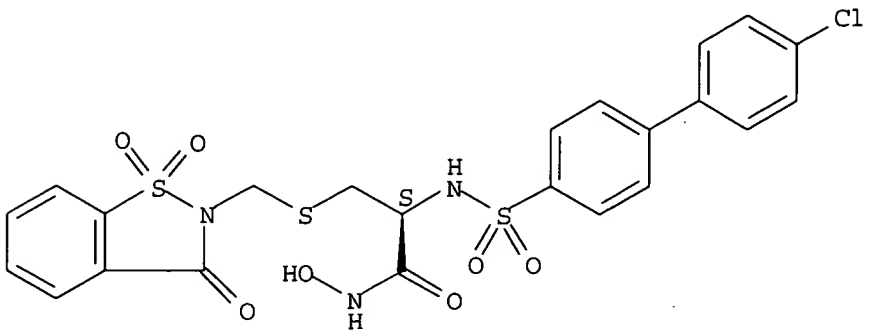
Absolute stereochemistry.



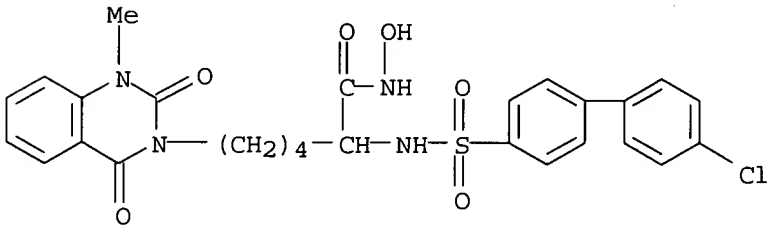
RN 240135-47-1 CAPLUS

CN Propanamide, 2-[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-3-[[(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)methyl]thio]-N-hydroxy-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

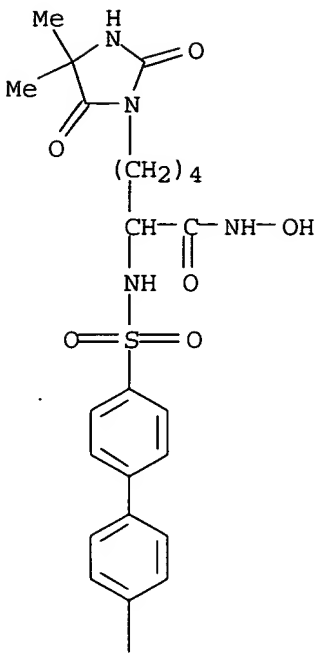


RN 240135-50-6 CAPLUS
CN 3(2H)-Quinazolinehexanamide, α-[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-1,4-dihydro-N-hydroxy-1-methyl-2,4-dioxo- (9CI) (CA INDEX NAME)



RN 240135-51-7 CAPLUS
CN 1-Imidazolidinehexanamide, α-[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-4,4-dimethyl-2,5-dioxo- (9CI) (CA INDEX NAME)

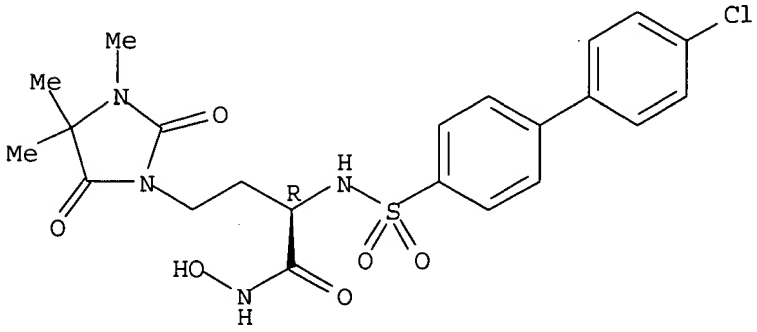
PAGE 1-A



PAGE 2-A

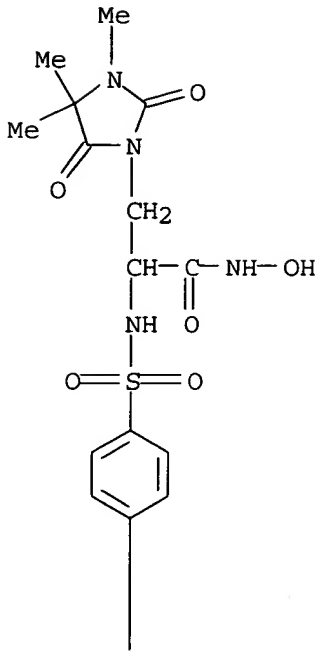
RN 240135-55-1 CAPLUS
CN 1-Imidazolidinebutanamide, α-[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3,4,4-trimethyl-2,5-dioxo-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 240135-58-4 CAPLUS
CN 1-Imidazolidinepropanamide, α-[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3,4,4-trimethyl-2,5-dioxo- (9CI) (CA INDEX NAME)

PAGE 1-A



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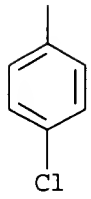
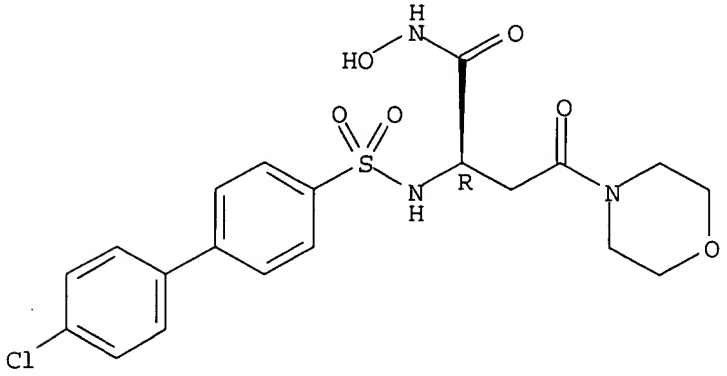


RN 240135-62-0 CAPLUS
CN 4-Morpholinebutanamide, α-[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-γ-oxo-, (αR)- (9CI) (CA INDEX NAME)

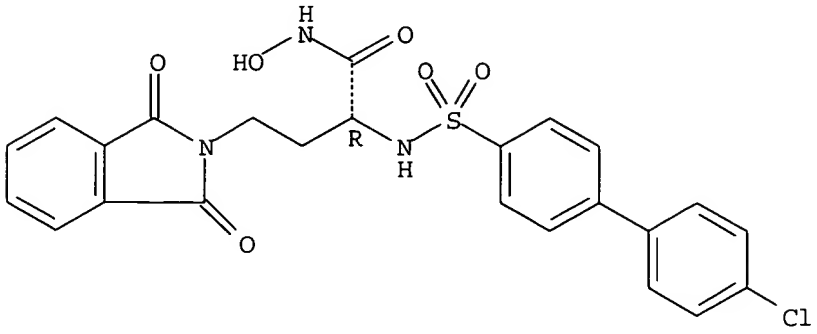
Absolute stereochemistry.



RN 355021-36-2 CAPLUS
CN 2H-Isoindole-2-butanamide, α-[[(4'-chloro[1,1'-biphenyl]-4-

yl)sulfonyl]amino]-1,3-dihydro-N-hydroxy-1,3-dioxo-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

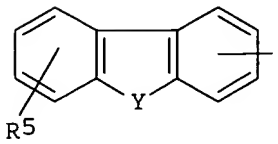



RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:137181 CAPLUS
DN 134:178144
TI Preparation of sulfonamido- and sulfinamido-containing carboxylic and hydroxamic acids derived from α,α'-disubstituted amino acids useful as matrix metalloproteinase inhibitors
IN Conrad, Christopher Alan; O'Brien, Patrick Michael; Ortwine, Daniel Fred; Picard, Joseph Armand; Sliskovic, Drago Robert
PA Warner-Lambert Company, USA
SO PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2001012592 | A2 | 20010222 | WO 2000-US21884 | 20000810 |
| | WO 2001012592 | A3 | 20010705 | | |
| | W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| | CA 2378332 | AA | 20010222 | CA 2000-2378332 | 20000810 |
| | BR 2000013390 | A | 20020430 | BR 2000-13390 | 20000810 |
| | EP 1210326 | A2 | 20020605 | EP 2000-955435 | 20000810 |
| | EP 1210326 | B1 | 20040225 | | |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| | TR 200200410 | T2 | 20020621 | TR 2002-200200410 | 20000810 |
| | TR 200202163 | T2 | 20021121 | TR 2002-200202163 | 20000810 |
| | TR 200202164 | T2 | 20021121 | TR 2002-200202164 | 20000810 |
| | TR 200202165 | T2 | 20021121 | TR 2002-200202165 | 20000810 |
| | TR 200202211 | T2 | 20021121 | TR 2002-200202211 | 20000810 |
| | JP 2003507362 | T2 | 20030225 | JP 2001-516893 | 20000810 |
| | AT 260251 | E | 20040315 | AT 2000-955435 | 20000810 |
| | PT 1210326 | T | 20040730 | PT 2000-955435 | 20000810 |
| | US 6677355 | B1 | 20040113 | US 2002-49544 | 20020213 |
| PRAI | US 1999-149660P | P | 19990818 | | |

WO 2000-US21884 W 20000810
OS MARPAT 134:178144
GI



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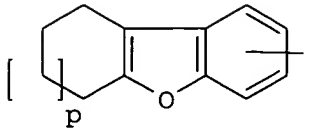

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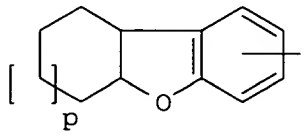

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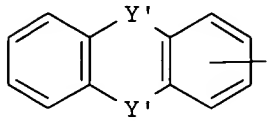


IV

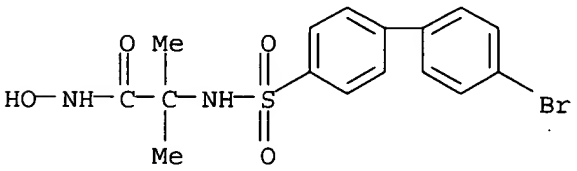
AB R1S(O)dNR2CR3R4C(O)X (I; e.g. 1-(dibenzofuran-3-sulfonylamino)cyclohexanecarboxylic acid) or a pharmaceutically acceptable salt thereof are useful for inhibiting matrix metalloproteinase enzymes in animals, and as such, prevent and treat diseases resulting from the breakdown of connective tissues. In I, X = OH, NHOH; R1 = II, III, IV, 4-ArMpiperidino, 4-Arpiperazino, 4-(N-(4-R5phenyl)-4-piperidinyl)phenyl, 4-(4-(4-R5phenyl)piperazino)phenyl, V; Y = O, S, -S(O)d (d = 1, 2), CH2, C(O), and NRq (Rq = H, C1-6 alkyl, or C1-6 alkylphenyl) ; each Y' = O, S, SO2, CH2, C(O), and NH; M = O, S, CH2; R5 = H, C1-10 alkyl, CF3, CONH2, halo, CN, COOH, C1-4 alkoxy, CHO, NO2, OH, (CH2)pOH, (CH2)pNH2, Ar, and NH2; p = 0-3; Ar = (a) phenyl; (b) Ph substituted with C1-4 alkyl, C, C1-4 alkoxy, halo, NH2, NO2, CN, COOH, CONH2, CF3, or COOR6 (R6 = C1-10 alkyl); and (c) heteroaryl; R2 = (a) H; (b) C1-4 alkyl; (c) benzyl; and (d) benzyl substituted with ≥1 C1-4 alkyl, C1-4 alkoxy, F, Cl, Br, I, NH2, NO2, CN, carboxy, and CO2R7 (R7 = H or C1-4 alkyl); and R3 and R4 are either (1) C1-20 alkyl; C3-10 cycloalkyl; phenyl; Ph substituted with C1-4 alkyl, C1-4 alkoxy, halo, NH2, NO2, CN, COOH, CO2R7, or CF3; C3-10 heterocyclic; and heteroaryl; or (2) substituents taken together to form a group of the empirical formula -(CH2)sZg-, wherein said substituents form a ring including the carbon atom adjacent the carbonyl group in I, and wherein s = 2-10; g = 0-6; and each Z is located at any position of said substituents and each Z = O, S, and NR8 (R8 = H, C1-3 alkyl). Also disclosed are pharmaceutical compns. and methods of treating diseases in which matrix metalloproteinases are involved including multiple sclerosis, atherosclerotic plaque rupture, restenosis, aortic aneurysm, heart failure, periodontal disease, corneal ulceration, burns, decubital ulcers, chronic ulcers or wounds, cancer metastasis, tumor angiogenesis, osteoporosis, rheumatoid or osteoarthritis, renal disease, left ventricular dilation, or other autoimmune or inflammatory diseases dependent upon tissue invasion by leukocytes. Other diseases for which I are claimed effective are: stroke, head trauma, spinal cord injury, Alzheimer's disease, amyotrophic lateral sclerosis, cerebral amyloid angiopathy, AIDS, Parkinson's disease, Huntington's disease, prion diseases, myasthenia gravis, and Duchenne's muscular dystrophy. Results of measurement of IC50 for matrix metalloproteinase enzyme inhibition are presented for 7 examples of I. Although the methods of preparation are not claimed, 33 example prepns. are included.

IT **326499-75-6P**, 2-(4'-Bromobiphenyl-4-sulfonylamino)-N-hydroxy-2-methylpropionamide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of sulfonamido- and sulfinamido-containing carboxylic and

hydroxamic acids derived from α,α'-disubstituted amino acids useful as matrix metalloproteinase inhibitors)

RN 326499-75-6 CAPLUS

CN Propanamide, 2-[[(4'-bromo[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



L13 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2000:3495 CAPLUS

DN 132:231496

TI Structure-activity relationships and pharmacokinetic analysis for a series of potent, systemically available biphenylsulfonamide matrix metalloproteinase inhibitors

AU O'Brien, Patrick M.; Ortwine, Daniel F.; Pavlovsky, Alexander G.; Picard, Joseph A.; Sliskovic, Drago R.; Roth, Bruce D.; Dyer, Richard D.; Johnson, Linda L.; Man, Chiu Fai; Hallak, Hussein

CS Departments of Chemistry Biochemistry and Pharmacokinetics/Drug Metabolism, Parke-Davis Pharmaceutical Research Division of Warner Lambert Company, Ann Arbor, MI, 48105, USA

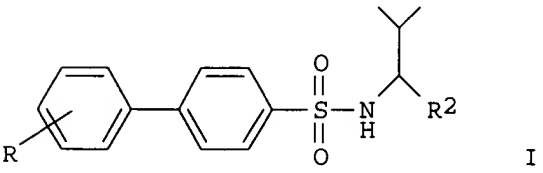
SO Journal of Medicinal Chemistry (2000), 43(2), 156-166
CODEN: JMCMAR; ISSN: 0022-2623

PB American Chemical Society

DT Journal

LA English

GI



I

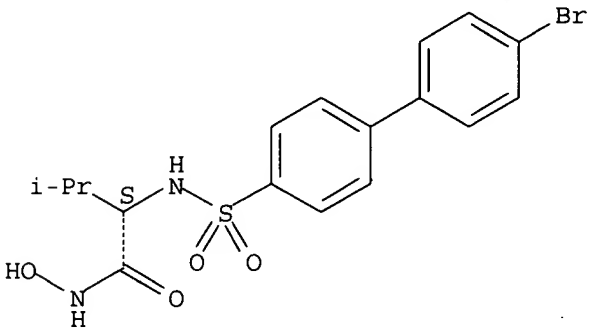
AB A series of biphenylsulfonamide derivs. of (S)-2-(biphenyl-4-sulfonylamino)-3-methylbutyric acid (I) were prepared and evaluated for their ability to inhibit matrix metalloproteinases (MMPs). For this series of compds., our objective was to systematically replace substituents appended to the biphenyl and α-position of 5 with structurally diverse functionalities to assess the effects these changes have on biol. and pharmacokinetic activity. The ensuing structure-activity relationship (SAR) studies showed that biphenylsulfonamides substituted with bromine in the 4'-position (II) significantly improved in vitro activity and exhibited superior pharmacokinetics (Cmax, t1/2, AUCs), relative to compound I. Varying the lipophilicity of the α-position by replacing the iso-Pr group of II with a variety of substituents, in general, maintained potency vs. MMP-2, -3, and -13 but decreased the oral systemic availability. Subsequent evaluation of its enantiomer, (R-isomer) of II, showed that both compds. were equally effective MMP inhibitors. In contrast, the corresponding hydroxamic acid enantiomeric pair, (III) and (R-isomer) of III,

stereoselectivity inhibited MMPs. For the first time in this series, (R-isomer) of III provided nanomolar potency against MMP-1, -7, and -9 (IC50's = 110, 140, and 18 nM, resp.), whereas III was less potent against these MMPs (IC50's = 24, 78, and 84 μM, resp.). However, unlike II, compound 16a' afforded very low plasma concns. following a single 5 mg/kg oral dose in rat. Subsequent X-ray crystal structures of the catalytic domain of stromelysin (MMP-3CD) complexed with inhibitors from closely related series established the differences in the binding mode of carboxylic acid-based inhibitors II and (R-isomer) of II relative to the corresponding hydroxamic acids III and (R-isomer) of III.

IT **261625-44-9P 261625-46-1P 261625-48-3P**
**261625-50-7P**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(biphenylsulfonamide MMP inhibitors SAR and pharmacokinetic anal.)

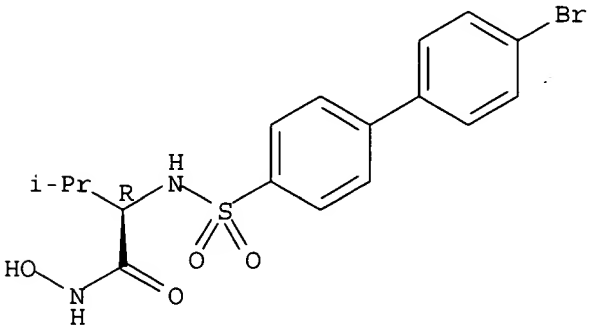
RN 261625-44-9 CAPLUS
CN Butanamide, 2-[[(4'-bromo[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3-methyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



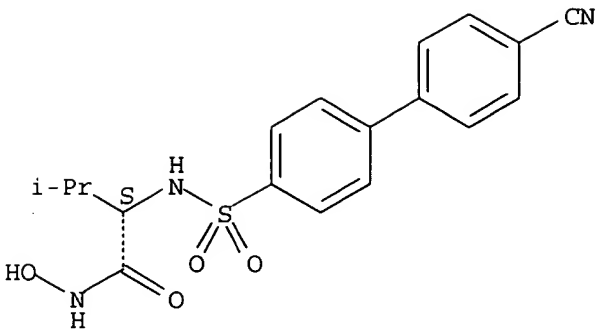

RN 261625-46-1 CAPLUS
CN Butanamide, 2-[[(4'-bromo[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



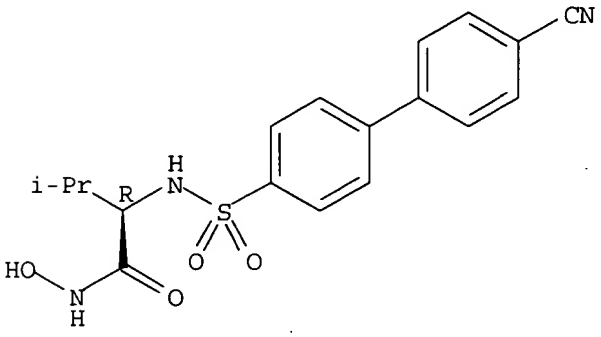

RN 261625-48-3 CAPLUS
CN Butanamide, 2-[[(4'-cyano[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3-methyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 261625-50-7 CAPLUS
CN Butanamide, 2-[[(4'-cyano[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:549253 CAPLUS
DN 131:184961
TI Preparation of 1,2-benzisothiazole, quinazoline, imidazole, and morpholine sulfonylamino derivatives as matrix-degrading metalloproteinase inhibitors
IN Kukkola, Paivi Jaana; Robinson, Leslie Anne; Sakaki, Junichi; Nakajima, Motowo
PA Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SO PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 9942443 | A1 | 19990826 | WO 1999-EP646 | 19990202 |

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

| | | | | | |
|---|---|---|---|---|---|
| | CA 2318145 | AA | 19990826 | CA 1999-2318145 | 19990202 |
| | AU 9929235 | A1 | 19990906 | AU 1999-29235 | 19990202 |
| | AU 747911 | B2 | 20020530 | | |
| | EP 1053226 | A1 | 20001122 | EP 1999-910174 | 19990202 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO | | | | |
| | BR 9909322 | A | 20001205 | BR 1999-9322 | 19990202 |
| | TR 200002224 | T2 | 20001221 | TR 2000-200002224 | 19990202 |
| | JP 2002503720 | T2 | 20020205 | JP 2000-532395 | 19990202 |
| | NZ 505968 | A | 20030328 | NZ 1999-505968 | 19990202 |
| | RU 2208609 | C2 | 20030720 | RU 2000-123166 | 19990202 |
| | NO 2000003565 | A | 20001003 | NO 2000-3565 | 20000711 |
| | US 6410580 | B1 | 20020625 | US 2000-601462 | 20000802 |
| PRAI | US 1998-18819 | A | 19980204 | | |
| | WO 1999-EP646 | W | 19990202 | | |

OS MARPAT 131:184961

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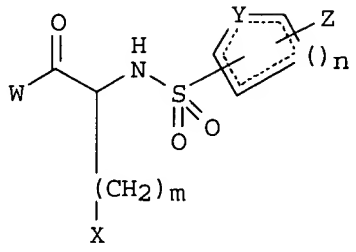
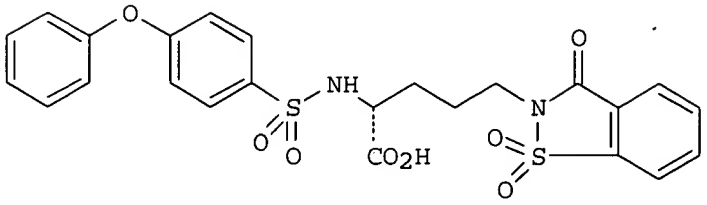


I



II

AB 1,2-Benzisothiazole, quinazoline, imidazole, and morpholine sulfonylamino derivs. (I) [wherein W = OH or NHOH; X = (un)substituted heterocycle, NR1SO2R2, hetercyclylalkylthio, CONR2R3, or NR1COR2; Y = C, N, O, or S, provided that when Y = C, n = 2; Z = (un)substituted alkyl, (hetero)aryl, alkoxy, (hetero)aryloxy, or heterocyclyl, CONR2R3, NR1COR2, NR1CONR2R3, OCONR2R3, NR1COOR4, or SO2R2Z; R1, R2, R3, R4 = independently H, (aryl)alkyl, heterocyclylalkyl, heteroarylalkyl, or R2 and R3 taken together with the N to which they are attached form a 5- to 7-membered (un)substituted ring; m = 1-6; n = 1 or 2] were prepared as matrix-degrading metalloproteinase inhibitors for treatment of inflammatory conditions, osteoarthritis, rheumatoid arthritis, and tumors (no data). Thus, (2R)-(BOC-amino)-5-iodopentanoic acid t-Bu ester was added to a solution of saccharin in 18-crown-6 and DMF followed by addition of DMF to yield (2R)-t-butoxycarbonylamino-5-(1,1,3-trioxo-2,3-dihydrobenzoisothiazol-2-yl)pentanoic acid t-Bu ester. The amide was deprotected by treatment with TFA in methylene chloride to give the amine. 4-Phenoxybenzenesulfonyl chloride (preparation given) was added to (2R)-amino-5-(1,1,3-trioxo-2,3-dihydrobenzoisothiazol-2-yl)pentanoic acid t-Bu ester in dioxane and TEA to form the sulfonamide followed by deesterification to yield (2R)-(4-phenoxybenzenesulfonylamino)-5-(1,1,3-trioxo-2,3-dihydrobenzisothiazol-2-yl)pentanoic acid (II).

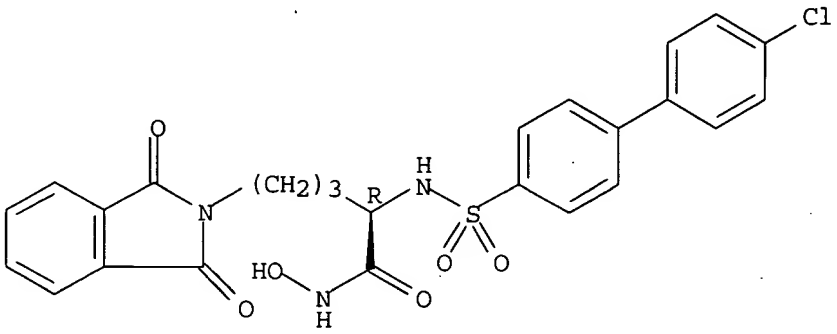
IT **240135-19-7P 240135-35-7P 240135-36-8P**
**240135-47-1P 240135-50-6P 240135-51-7P**
**240135-55-1P 240135-58-4P 240135-62-0P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 1,2-benzisothiazole, quinazoline, imidazole, and morpholine sulfonylamino derivs. as matrix-degrading metalloproteinase inhibitors)

RN 240135-19-7 CAPLUS

CN 2H-Isoindole-2-pentanamide, α-[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-1,3-dihydro-N-hydroxy-1,3-dioxo-, (αR)- (9CI) (CA INDEX NAME)

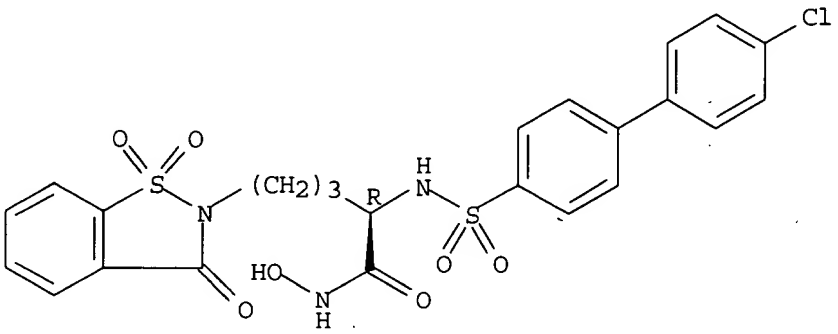
Absolute stereochemistry.




RN 240135-35-7 CAPLUS

CN 1,2-Benzisothiazole-2(3H)-pentanamide, α-[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3-oxo-, 1,1-dioxide, (αR)- (9CI) (CA INDEX NAME)

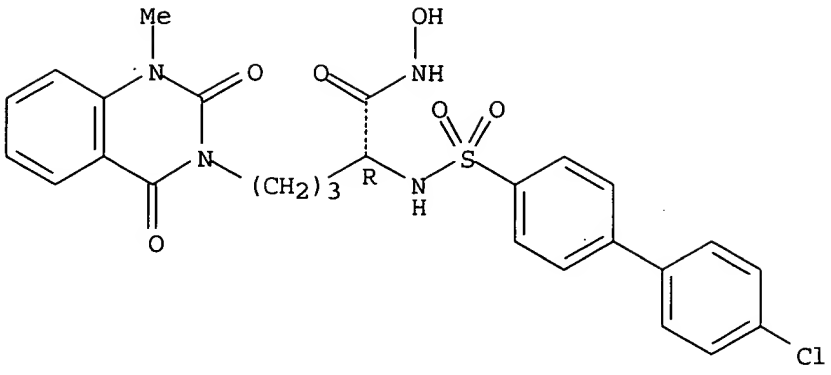
Absolute stereochemistry.




RN 240135-36-8 CAPLUS

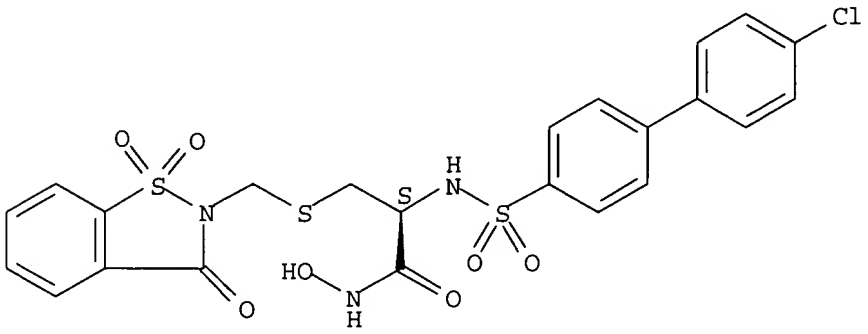
CN 3(2H)-Quinazolinepentanamide, α-[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-1,4-dihydro-N-hydroxy-1-methyl-2,4-dioxo-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

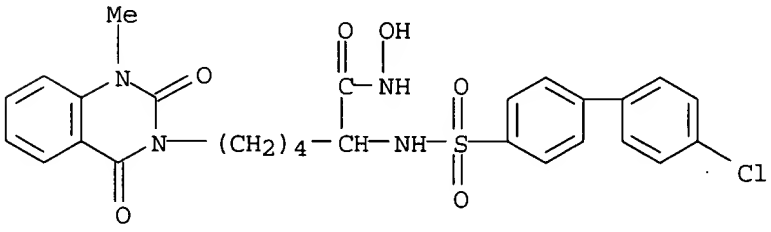


RN 240135-47-1 CAPLUS
CN Propanamide, 2-[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-3-[[(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)methyl]thio]-N-hydroxy-, (2S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 240135-50-6 CAPLUS
CN 3(2H)-Quinazolinehexanamide, α-[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-1,4-dihydro-N-hydroxy-1-methyl-2,4-dioxo- (9CI) (CA INDEX NAME)



RN 240135-51-7 CAPLUS
CN 1-Imidazolidinehexanamide, α-[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-4,4-dimethyl-2,5-dioxo- (9CI) (CA INDEX NAME)

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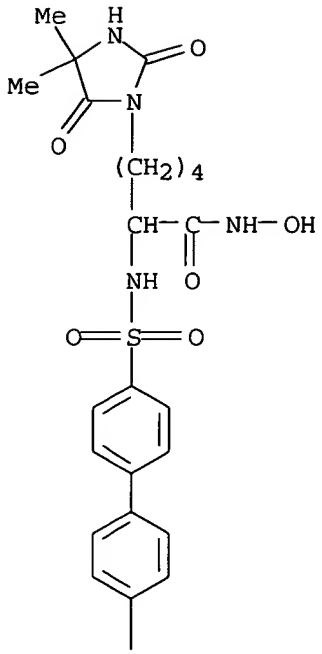

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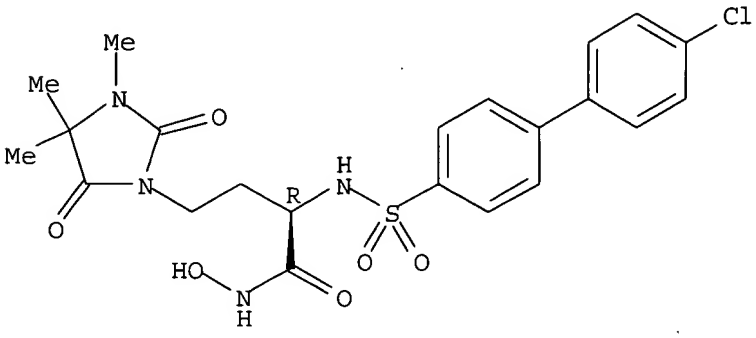
RN 240135-55-1 CAPLUS
CN 1-Imidazolidinebutanamide, α-[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3,4,4-trimethyl-2,5-dioxo-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 240135-58-4 CAPLUS
CN 1-Imidazolidinepropanamide, α-[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-3,4,4-trimethyl-2,5-dioxo- (9CI) (CA INDEX NAME)

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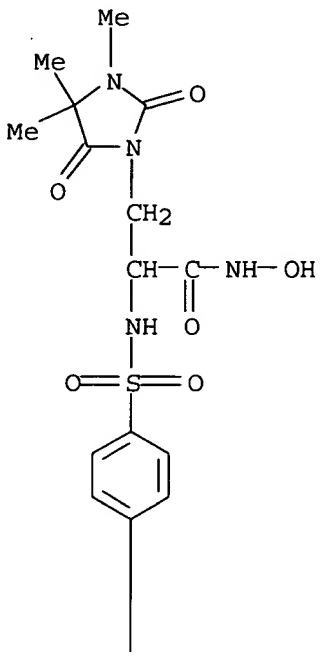

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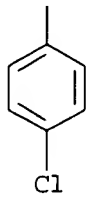
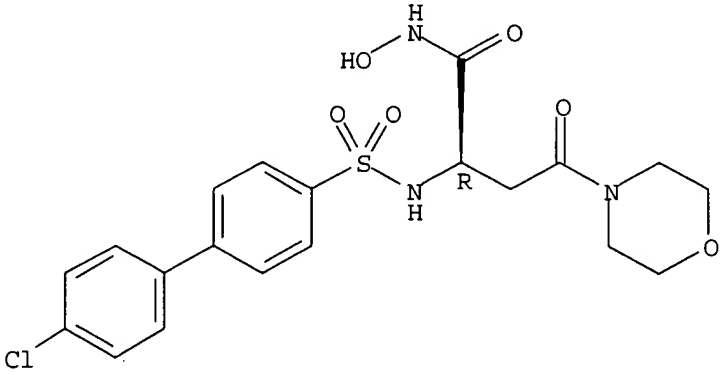


RN 240135-62-0 CAPLUS
CN 4-Morpholinebutanamide, α-[[(4'-chloro[1,1'-biphenyl]-4-yl)sulfonyl]amino]-N-hydroxy-γ-oxo-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT